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1213 172

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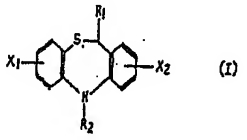
(54) DIBENZOTHIAZEPINE DERIVATIVES AND PRODUCTION OF THE SAME

(71) We, FUJISAWA PHARMACEUTICAL CO. LTD., a Japanese Body Corporate, of 3, Doshomachi 4-chome, Osaka, Japan, do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to dibenzothiazepine derivatives and salts thereof, and to processes for the preparation thereof.

In accordance with the invention there is provided a dibenzothiazepine derivative of the formula (I):



(I)

wherein each of X_1 and X_2 is a hydrogen or halogen atom; R_1 is an alkyl, cycloalkyl, haloalkyl or aralkyl group or an alkyl group substituted with R_3 in which R_3 is an amino, alkylamino, dialkylamino or saturated 5 to 7 membered N-heterocyclic group; and R_2 is a hydrogen atom or an alkyl, cycloalkyl, haloalkyl or aralkyl group or an alkyl group substituted with an R_3 group as defined above, provided that at least one of R_1 and R_2 is an alkyl group substituted with R_3, and non-toxic acid addition and quaternary ammonium salts thereof.

In the above and subsequent description and claims of this invention, the term "halogen" and the halogen atom in the term "haloalkyl" and "haloaryl" mean fluorine, chlorine, bromine and iodine; the term "alkyl" means a straight or branched chain alkyl group having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl; the term "cycloalkyl" means saturated monocyclic monovalent hydrocarbon group such as cyclohexyl; the alkyl radical in the term "haloalkyl," "alkylamino", "dialkylamino" "alkyl substituted with R_3", "alkylamino" and "hydroxyalkylimino" means a straight or branched chain alkyl group having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl; the term "aralkyl" and the aralkyl radical in the term "aralkylimino" mean an alkyl group substituted by a monocyclic aromatic monovalent hydrocarbon group such as benzyl, phenethyl, α-methylbenzyl, phenylpropyl, tolylmethyl and xylylmethyl; the term "aryl" and the aryl radical in the term "haloaryl" and "arylimino" mean a monocyclic aromatic monovalent hydrocarbon group such as phenyl, tolyl and xylyl; the term "a saturated 5 to 7 membered N-heterocyclic radical" means a nitrogeneous monocyclic one which may be substituted with hydroxy and either aryl or haloaryl, and whose carbon chain may be interrupted or not with oxo, imino, alkylimino, hydroxyalkylimino, aralkylimino or arylimino groups, such as 1-pyrroli-

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dinyl, 1-pyrazolidinyl, 1-oxazolidinyl, piperidino, 1-piperazinyl, 4-methyl (or ethyl)-1-piperazinyl, 4-hydroxyethyl (or hydroxymethyl)-1-piperazinyl, 4-benzyl-1-piperazinyl, 4-phenyl-1-piperazinyl, 4-hydroxy-4-phenyl-piperidino, 4-hydroxy-4-(4-chlorophenyl)piperidino, morpholino and 1-azepinyl.

The salts of the dibenzothiazepine derivatives (I), are non-toxic acid addition salts as well as quaternary ammonium salts thereof. Examples of the non-toxic acid addition salts are the salts with an inorganic acid such as hydrochloric acid, hydrobromic acid and sulfuric acid, and with an organic acid such as maleic acid, tartaric acid, citric acid, succinic acid, picric acid and *p*-toluenesulfonic acid. Examples of the quaternary ammonium salts are the salts with alkyl halides such as methyl chloride, methyl bromide, methyl iodide, ethyl chloride, ethyl bromide, ethyl iodide and propyl iodide, and with aralkyl halides such as benzyl chloride, benzyl bromide and phenethyl bromide.

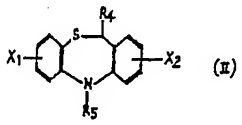
The compounds (I) of this invention are novel and of great worth medically. More particularly, they possess, for instance, a potent reserpine — antagonistic activity and are useful as antidepressants.

The compounds (I) of this invention may be administered orally and parenterally in the therapeutical use. The pharmaceutically useful compositions containing the compounds (I) together with a significant amount of a non-toxic solid or liquid carrier are also included within the scope of this invention. In such compositions are included solid compositions such as tablets, pills, dispersible powders and granules, and liquid compositions such as injectable solutions, orally administrable solutions and suspensions.

In solid compositions one or more of the active compounds is or are admixed with an inert diluent such as potato starch, lactose, calcium phosphate and further additional substances, if needed, such as lubricants, e.g. magnesium stearate; binders, e.g. gelatine; and disintegrators, e.g. cellulose and calcium glycolate. In solid compositions, are included capsules of absorbable material such as gelatine containing one or more active compounds with or without the addition of diluents or excipients, and also suppositories for rectal administration containing one or more active compounds for which bases are exemplified by cacao butter, glycerogelatin, polyvinylalcohol and hardened vegetable oil.

The compounds (I) of this invention may be prepared basically by alkylation of an appropriate dibenzothiazepine compound in which there is a replaceable hydrogen atom at the 5 and/or 11 position of dibenzothiazepine ring, or by cyclisation an appropriate amino benzylthiophenol derivative.

More specifically, the compounds (I) may be prepared by treating a compound of the formula (II):



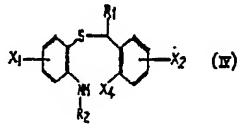
(II)

wherein X_1 and X_2 are as defined in the formula (I), R_4 is hydrogen, alkyl, cycloalkyl, haloalkyl, aralkyl or alkyl substituted with R_3, and R_5 is hydrogen, alkyl, cycloalkyl, haloalkyl, aralkyl or alkyl substituted with R_3 in which R_3 is the same meaning as defined in the formula (I), provided that at least one of R_4 and R_5 is hydrogen,

with an organo lithium compound and an alkylating agent of the formula (III):

$$R_6—X_3 \qquad \text{(III)}$$

wherein R_6 has the same meaning as R_1 above and X_3 is an acid residue, or with an alkylating agent of the formula (III) in the presence of an alkaline condensing agent, and, if necessary, treating the resultant compound (I) in which R_1 or R_2 is haloalkyl with an amine of the formula: R_3—H wherein R_3 has the meaning given above. Alternatively, the compounds (I) may be obtained by ring-closing with heating a compound of the formula (IV):



(IV)

wherein X_1, X_2, R_1 and R_2 are as defined above, and X_4 is an acid residue.

The compounds (II) and (IV) used as the starting compounds include known and unknown ones, and the compounds (IV) may be obtained, for instance, by the reaction of a 2-aminothiophenol derivative and a 2-halobenzyl halide derivative and the compounds (II) may be prepared by cyclisation of an appropriate 2-aminobenzylthiophenol derivative.

The reactions for the production of the compound (I) of this invention will hereinafter be illustrated in detail.

Alkylation

(1) C-Alkylation

This alkylation is substantially concerned with the replacement of the hydrogen atom at the 11 position of the compound (II) with the group R_6, wherein R_6 has the same definition as R_1 in the formula (I). The reaction is carried out by treating the compound (II) wherein R_4 is hydrogen, with an organic lithium compound and an alkylating agent to give the desired compound (I).

As an organic lithium compound to be used, there are included an alkyl lithium (e.g. methyl, ethyl, propyl, isopropyl, butyl or isobutyl lithium) aryl lithium (e.g. phenyl, tolyl, xylyl or naphthyl lithium) and aralkyl lithium (e.g. benzyl, phenethyl, phenylpropyl or tolylmethyl lithium).

The alkylating agents as used herein are reactive esters of alkyl alcohols (or cycloalkyl, haloalkyl, aralkyl or R_3-alkyl alcohols) which are representable by the formula R_6—X_3 (III) wherein R_6 has the same meaning as R_1 of the formula (I) and X_3 is an acid residue. "R_3-alkyl" as used herein and herinafter means alkyl substituted with R_3.

Examples of the alkylating agents are alkyl, cycloalkyl, haloalkyl, aralkyl and R_3-alkyl halides (chloride, bromide and iodide); alkyl, cycloalkyl, haloalkyl, aralkyl and R_3-alkyl *p*-toluenesulfonates; and alkyl, haloalkyl, aralkyl and R_3-alkyl sulfonates, among which the halides are preferably used in this reaction.

When using a haloalkyl halide, it is desirable to select one having two different halogens such as a chloroalkyl bromide, chloroalkyl iodide or bromoalkyl iodide.

The reaction is generally, but not essentially, carried out in a solvent such as ether, *n*-hexane, benzene or other inert solvent, and at room temperature or approximately at the boiling point of solvent to be used.

Furthermore, as a reaction mechanism in this reaction, it is considered that the compound (II) as the starting compound is firstly reacted with an organic lithium compound, thereby to substitute a hydrogen atom in methylene part at the 11 position of the compound (II) with lithium, and then the lithium substitution product is reacted with an alkylating agent, thereby to substitute lithium with the alkyl part of the alkylating agent. Accordingly, it is preferable to treat firstly the compound (II) with an organic lithium compound and then the resultant mixture with an alkylating agent.

(2) N-Alkylation

This alkylation is substantially concerned with the replacement of the hydrogen atom attached to nitrogen atom at the 5 position of the compound (II), with a group R_6 wherein R_6 is as defined above.

It is conducted by treating the compound (II) wherein R_5 is hydrogen, with an alkylating agent in the presence of an alkaline condensing agent to give the desired compound (I).

A few examples of the alkaline condensing agent to be used herein are alkali metals (e.g. sodium and potassium), alkaline earth metals (e.g. magnesium, calcium and barium), or their hydroxides, hydrides, alkoxides or carbonates. The alkylating agent used in this reaction may be the same one as described in the C-alkylation. The reaction is usually conducted in a solvent such as liquid ammonia, dimethylformamide, dimethylsulfoxide, methanol, ethanol or any other inert solvent. These solvents may be employed mixed with each other. The reaction temperature varies in accordance with the kind of the starting compound (II), the alkaline condensing agent and the solvent used. The reaction is generally effected approximately at the boiling point of the solvent to be used, but when using dimethylformamide or liquid ammonia, it may be effected at lower temperature.

When a compound (I) in which R_1 or R_2 is haloalkyl, is produced in the above-mentioned alkylations, it can be converted into the corresponding compound (I) in which R_1 or R_2 is R_3-alkyl, by treatment with an amine of the formula: R_3H wherein R_3 is as defined in the formula (I).

The amine is ammonia or a monoalkylamine, dialkylamine or saturated 5 to 7 membered N-heterocyclic compound.

The reaction may be carried out in a solvent such as benzene, toluene, xylene, chloroform or any other inert solvent. When the amine used is liquid, it may act as a solvent.

Ring-Closure

This ring-closing reaction may be conducted by heating the compound (IV) to obtain the object compound (I).

The acid residue in the definition X_4 of the compound (IV) means a residue of an acid such as a hydrohalic acid (e.g. hydrochloric acid, hydrobromic acid or hydroiodic acid), sulfuric acid, an alkylsulfuric acid or *p*-toluenesulfonic acid. The ring-closing reaction may advantageously be achieved in the presence of an alkaline condensing agent. The alkaline condensing agent to be used herein may be the same agent as employed in the N-alkylation.

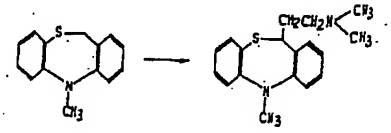
The reaction is ordinarily carried out in a solvent such as pyridine, picoline, dimethylaniline, trimethylamine, triethylamine or dimethylformamide. When the starting compound (IV) possesses halogen as an acid residue, the reaction may be accelerated by the addition of a dehydrohalogenation catalyst such as copper powder. It is generally effected at the neighborhood of the boiling point of the solvent used. If it is desired to carry out the reaction at higher-temperature, a solvent having high-boiling point is used.

Though the object compound (I) may be prepared by any reaction mentioned above, it is preferred, for the purpose of economical production of the compound (I), to select a suitable one from the above reactions or use a combination thereof, depending upon the kind of halogen atom on the benzene ring as well as the substituent(s) at the 11 position or the 5 and 11 positions of the desired compound (I). For instance, the compound (I) in which R_1 is R_3-alkyl can advantageously be obtained by the C-alkylation of the starting compound (II) wherein R_4 is hydrogen, with an R_3-alkyl halide or the C-alkylation of said compound (I) with a haloalkyl halide and then amination of the resultant product. When the compound (II) in which X_1 and/or X_2 is bromine or iodine is used in the C-alkylation, there is a possibility of said halogen being substituted with lithium during this reaction. Accordingly, it is proposed to employ the N-alkylation or ring-closing reaction as explained hereinabove as an advantageous method for preparing the object compound (I) in which X_1 and/or X_2 is bromine or iodine.

Thus obtained compound (I) may be converted into a corresponding acid addition or quaternary ammonium salt by treatment with an organic or inorganic acid or with an alkyl or aralkyl halide.

The following specific examples illustrate the production of representative compounds of this invention.

EXAMPLE 1-(1)



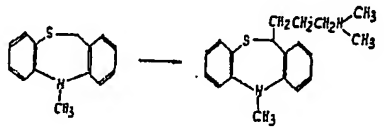
To a mixture of lithium metal (410 mg.) in ether, was added bromobenzene (4.7 g.) and the mixture heated under reflux till the floating lithium metal disappeared. The ether solution of phenyl lithium thus prepared, was dropwise added to a solution of 5-methyl-5,11-dihydro dibenzo[b,e][1,4] thiazepine (6.1 g.) in ether (60 c.c.) and then the mixture was stirred at room temperature for 3 hours. To this mixture was added 2-dimethylaminoethyl chloride (6.0 g.) and the mixture was heated under reflux for 5 hours. After cooling, the remaining lithium was filtered off. The ether layer was washed with water and further extracted with a 10% hydrochloric acid aqueous solution. The hydrochloric acid extract was neutralized with a 10% sodium hydroxide aqueous solution and the precipitating oil was extracted with chloroform. The chloroform extract was condensed and thus obtained oily substance was distilled under reduced pressure to obtain an oil (25 g.) as a distillate at 180—182°C/0.9 mmHg. This oil was treated according to the conventional method for

preparing an acid addition salt to obtain 5 - methyl - 11 - (2 - dimethylaminoethyl)-5,11 - dihydrodibenzo[b,e][1,4]thiazepine maleate having mp. 170—172°C. (decomp).

Analysis calculated for $C_{18}H_{22}N_2S \cdot C_4H_4O_4$

C 63.75, H 6.32, N 6.72, S 7.72,
Found: C 63.28, H 6.28, N 6.59, S 7.59.

EXAMPLE 1-(2)



To an ether solution of phenyl lithium prepared by the reaction of lithium metal (0.41 g.) and bromobenzene (4.7 g.) in ether according to the conventional method, was dropwise added 5-methyl-5,11-dihydro dibenzo[b,e][1,4] thiazepine (6.1 g.) in ether (60 c.c.), after which the mixture was stirred at room temperature for 3 hours. To this mixture was added 3-dimethylaminopropyl chloride (6.0 g.) and the reaction mixture was heated under reflux for 5 hours.

This reaction mixture was treated in the same manner as described in Example 1-(1) to obtain 5 - methyl - 11 - (3 - dimethylaminopropyl) - 5,11 - dihydro dibenzo-[b,e][1,4] thiazepine (2.5 g.) as an oil.

Analysis calculated for $C_{11}H_{24}N_2S$

N 8.97, S 10.24,
Found: N 8.87; S 10.20.

According to the procedure of Examples 1-(1) and -(2) described above, the following compounds were obtained.

5-Methyl-11-(2-diethylaminoethyl)-5,11-dihydro dibenzo[b,e][1,4] thiazepine, an oil,

Analysis calculated for $C_{20}H_{26}SN_2$

C 73.59, H 8.03, N 8.58,
Found: C 73.29, H 7.95, N 8.60.

5-Methyl-11-(1-methyl-2-morpholinoethyl)-5,11-dihydro dibenzo[b,e][1,4] thiazepine, an oil as a distillate at bp. 240°C/0.5 mmHg.

Analysis calculated for $C_{21}H_{26}ON_2S$

C 71.14, H 7.39, N 7.90, S 9.05,
Found: C 71.04, H 7.19, N 8.01, S 9.00.

5-Methyl-11-(3-morpholinopropyl)-5,11-dihydro dibenzo[b,e][1,4]thiazepine, an oil.

Analysis calculated for $C_{21}H_{26}ON_2S$

C 71.14, H 7.39, N 7.90, S 9.05,
Found: C 71.40, H 7.45, N 8.15, S 9.10.

2-Chloro-5-methyl-11-(2-dimethylaminoethyl)-5,11-dihydro dibenzo[b,e][1,4] thiazepine, a yellowish viscous oil,

Analysis calculated for $C_{18}H_{21}N_2SCl$

C 64.94, H 6.51, N 8.39, S 9.63, Cl 10.65,
Found: C 65.04, H 6.54, N 8.38, S 9.79, Cl 10.80.

2-Chloro-5-methyl-11-(3-dimethylaminopropyl)-5,11-dihydro dibenzo[b,e][1,4] thiazepine, a yellow oil.

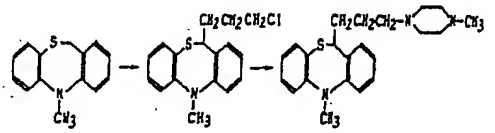
Analysis calculated for $C_{19}H_{23}N_2SCl$

C 65.78, H 6.68, N 8.07, S 9.29, Cl 10.22,
Found: C 65.80, H 6.59, N 8.20, S 9.41, Cl 9.98.

5-Methyl-11-[3-(1-pyrrolidinyl)propyl]-5,11-dihydro dibenzo[b,e][1,4] thiazepine, a reddish yellow oil.

Analysis calculated for $C_{21}H_{26}N_2S$
C 74.52, H 7.74, N 8.28, S 9.46,
Found: C 74.34, H 7.88, N 8.14, S 8.89.

EXAMPLE 2-(1)



To an ether solution of phenyl lithium prepared from phenyl bromide (2.5 g.), lithium (220 mg.) and absolute ether (22 c.c.), was added dropwise 5-methyl-5,11-dihydro dibenzo[b,e][1,4] thiazepine (2.0 g.) in benzene (22 c.c.). The mixture was stirred at room temperature for 3 hours and then 1-bromo-3-chloropropane (7.5 g.) was added. The reaction mixture was stirred at 50°C. for 3.5 hours and cooled, after which the remaining lithium was filtered off.

The reaction mixture was washed with water and then a 10% hydrochloric acid aqueous solution, and dried over anhydrous magnesium sulfate. The solvent was distilled off to obtain an oil, which was subjected to chromatograph using a column packed with alumina, where petroleum ether and then n-hexane were used as developing solvents and chloroform was applied as an eluting solvent. The eluting chloroform was condensed to obtain a yellow oil (2.0 g.).

The thus obtained oil (2.0 g.) was allowed to react with methylpiperazine (20 c.c.) at 120°C. for 17 hours. Water was added to the reaction mixture, which was then extracted with a mixture of benzene and ether. The extract was washed with water several times and further a 10% hydrochloric acid aqueous solution, and neutralized with a conc. sodium hydroxide solution and then extracted with chloroform. The chloroform layer was subjected to chromatograph using a column packed with alumina in the same manner as above to obtain an oil. This oil was distilled in an oil bath under reduced pressure to obtain 5 - methyl - 11 - [3 - (4 - methylpiperazinyl)propyl] - 5,11 - dihydro dibenzo[b,e][1,4]thiazepine as a distillate under 0.1—0.2 mmHg at 240—260°C.

Analysis calculated for $C_{22}H_{29}N_3S$
C 71.90, H 7.95, N 11.44, S 8.71,
Found: C 72.13, H 8.06, N 11.41, S 8.76.

Its maleate was recrystallized from 99% ethanol in the form of a pale yellow powder having mp. 185—186°C. (decomp.).

Analysis calculated for $C_{22}H_{29}N_3S \cdot 2C_4H_4O_4$
C 60.09, H 6.21, N 7.01,
Found: C 60.50, H 6.23, N 7.05.

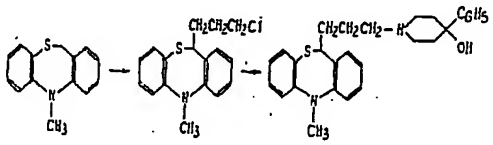
According to the procedure of Example 2-(1) described above, the following compound was obtained.

5 - Methyl - 11 - [2 - [4 - (2 - hydroxyethyl)piperazinyl]ethyl] - 5,11 - dihydro dibenzo[b,e][1,4] thiazepine, a reddish yellow viscous oil.

Analysis calculated for $C_{22}H_{29}N_3SO$
C 68.90, H 7.62, N 10.96, S 8.35,
Found: C 68.56, H 7.51, N 10.59, S 8.26.

Its hydrochloride melted at 238—240°C. (decomp.).
Analysis calculated for $C_{22}H_{29}N_3SO \cdot 2HCl$
C 57.89, H 6.85, N 9.21, S 7.02,
Found: C 58.23, H 6.74, N 9.36, S 7.07.

EXAMPLE 2-(2)

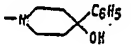


A similar procedure to Example 2-(1) was followed using a xylene solution of 4-hydroxy-4-phenylpiperidine. 5 - Methyl - 11 - [3 - (4 - hydroxy - 4 - phenylpiperidinyl)propyl] - 5,11 - dihydro dibenzo[b,e][1,4] thiazepine was obtained as an oil.

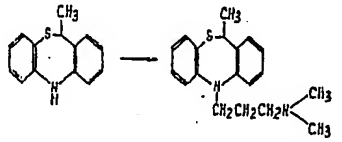
Infra-Red Spectrum:

3400 cm^{-1} (—OH)
2800 cm^{-1} (—N<)
670 cm^{-1} (mono substituted benzene)

Nuclear Magnetic Resonance Spectrum:

2.5—1.5	PPM		the hydrogen atom of methylene
3.20	PPM	singlet	N—CH_3
4.95	PPM	triplet	the hydrogen atom at the 11th position
7.2	PPM	singlet	
7.3—6.5	PPM		the hydrogen atom of benzene of dibenzothiazepine ring

EXAMPLE 3



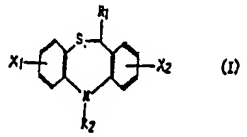
A solution of 11 - methyl - 5,11 - dihydro dibenzo[b,e] [1,4]thiazepine (2.1 g.) in absolute dimethylformamide (20 c.c.), was dropwise added, under ice-cooling, to a solution of sodium hydride (960 mg.) in absolute dimethylformamide (20 c.c.). The reaction was exothermic and the color of the reaction mixture changed to reddish brown. This reaction mixture was stirred at room temperature for an hour and then at 50°C for an hour. To this mixture was added a solution of N,N-dimethylaminopropyl chloride (1.2 g.) in dimethylformamide (10 c.c.) and the mixture was stirred at room temperature for an hour and then at 50°C for an hour. After cooling, the reaction mixture was poured into water and extracted with ether. The ether extract was washed with water and extracted with a 10% hydrochloric acid aqueous solution. The hydrochloric acid extract was cooled and neutralized with a 10% sodium hydroxide aqueous solution. The precipitating oil was extracted with ether and the ether extract was dried, after which the solvent was distilled off to obtain 5 - (3 - dimethylaminopropyl) - 11 - methyl - 5,11 - dihydro dibenzo[b,e] [1,4] thiazepine (0.5 g.) as an oil.

This oily substance was treated according to the conventional method for preparing an acid addition salt to obtain crystals of 5 - (3 - dimethylaminopropyl)-11 - methyl - 5,11 - dihydro dibenzo[b,e] [1,4]thiazepine oxalate having mp. 139—143°C. (decomp.).

Analysis calculated for $C_{19}H_{24}N_3S \cdot C_2H_2O_4$
C 62.66, H 6.51, N 6.96, S 7.97,
Found: C 62.77, H 6.72, N 6.93, S 8.12.

WHAT WE CLAIM IS:—

1. A dibenzothiazepine derivative of the formula:



wherein each of X_1 and X_2 is a hydrogen or halogen atom; R_1 is an alkyl, cycloalkyl, haloalkyl or aralkyl group or an alkyl group substituted with R_3 in which R_3 is an amino, alkylamino, dialkylamino or saturated 5 to 7 membered N-heterocyclic group; and R_2 is a hydrogen atom or an alkyl, cycloalkyl, haloalkyl or aralkyl group or an alkyl group substituted with an R_3 group as defined above, provided that at least one of R_1 and R_2 is an alkyl group substituted with R_3, and non-toxic acid-addition and quaternary ammonium salts thereof.

2. 5 - Methyl - 11 - (2 - dimethylaminoethyl) - 5,11 - dihydro dibenzo[b,e][1,4] thiazepine and the maleate thereof.

3. 2 - Chloro - 5 - methyl - 11 - (2 - dimethylaminoethyl) - 5,11 - dihydro dibenzo[b,e][1,4]thiazepine.

4. 5 - Methyl - 11 - (3 - dimethylaminopropyl) - 5,11 - dihydro dibenzo[b,e]-[1,4]thiazepine.

5. 2 - Chloro - 5 - methyl - 11 - (3 - dimethylaminopropyl) - 5,11 - dihydro dibenzo[b,e][1,4]thiazepine.

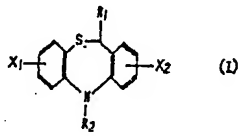
6. 5 - Methyl - 11 - [3 - (4 - methylpiperazinyl)propyl] - 5,11 - dihydro dibenzo[b,e][1,4]thiazepine and the maleate thereof.

7. 5 - Methyl - 11 - [2 - [4 - (2 - hydroxyethyl)piperazinyl]ethyl] - 5,11 - dihydro dibenzo[b,e][1,4]thiazepine and the hydrochloride thereof.

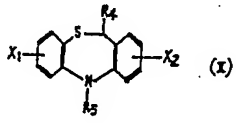
9. 5 - Methyl - 11 - (1 - methyl - 2 - morpholinoethyl) - 5,11 - dihydro dibenzo [b,e][1,4]thiazepine.

10. 5 - (3 - Dimethylaminopropyl) - 11 - methyl - 5,11 - dihydro dibenzo[b,e]-[1,4]thiazepine.

11. A process for the preparation of a dibenzothiazepine derivative of formula (I):



wherein each of X_1 and X_2 is a hydrogen or halogen atom; R_1 is an alkyl, cycloalkyl, haloalkyl or aralkyl group or an alkyl group substituted with R_3 in which R_3 is an amino, alkylamino, dialkylamino or saturated 5 to 7 membered N-heterocyclic group; and R_2 is a hydrogen atom or an alkyl, cycloalkyl, haloalkyl, aralkyl group or an alkyl group substituted with an R_3 group as defined above, provided that at least one of R_1 and R_2 is an alkyl group substituted with R_3, which comprises:
i) treating a compound of the formula (II):

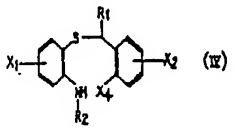


wherein X_1 and X_2 are as defined above, R_4 is a hydrogen atom or an alkyl, cycloalkyl, haloalkyl or aralkyl group or an alkyl group substituted with R_3, and R_5 is a hydrogen atom or an alkyl, cycloalkyl, haloalkyl or aralkyl group or an alkyl group substituted with R_3, in which R_3 is as defined above, provided that at least one of R_4 and R_5 is a hydrogen atom, with an organo-lithium compound and an alkylating agent of the formula (III):

$$R_6—X_3 \qquad \text{(III)}$$

wherein R_6 has the same meaning as R_1 described above and X_3 is an acid residue or with an alkylating agent of formula (III) in the presence of an alkaline condensing agent, to obtain the compound (I), or

ii) heating a compound of the formula (IV):



(IV)

wherein X_1, X_2, R_1 and R_2 are as defined above, and X_4 is an acid residue, to obtain the compound (I) and, if desired, converting the resultant compound (I) into the corresponding acid addition or quaternary ammonium salt.

12. A process according to claim 11, in which a compound of formula (II) wherein R_4 is a hydrogen atom is reacted with an organo-lithium compound and an alkylating agent of formula R_6—X_3, wherein R_6 and X_3 are as defined in claim 11.

13. A process according to claim 11, in which a compound of formula (II) wherein R_4 is a hydrogen atom is reacted with an organo-lithium compound and a haloalkyl halide and the resultant compound of formula (I) wherein R_1 is a haloalkyl group is further reacted with an amine of the formula: R_3—H wherein R_3 is as defined in claim 11, to obtain a compound of the formula (I) wherein R_1 is an alkyl group substituted with R_3.

14. A process according to claim 11, in which a compound of formula (II) wherein R_5 is a hydrogen atom is reacted with an alkylating agent of formula R_6—X_3, wherein R_6 and X_3 are as defined in claim 11, in the presence of an alkaline condensing agent.

15. A process according to claim 11, in which the alkylating agent is an alkyl, cycloalkyl, haloalkyl, aralkyl or R_3-alkyl halide, wherein R_3 is as defined in claim 11.

16. A process according to claim 11, in which the organo-lithium compound is an alkyl, aryl or aralkyl lithium.

17. A process for the preparation of a dibenzothiazepine derivative of formula (I) herein substantially as hereinbefore described with reference to the Examples.

18. Dibenzothiazepine derivatives of formula (I) herein whenever prepared by a process according to any one of claims 11 to 17.

19. A pharmaceutical composition comprising, as the active ingredient, a dibenzothiazepine derivative of formula (I) herein in admixture with a non-toxic solid or liquid carrier.

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